BIOGRAPHICAL SKETCH

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NAME: James D. Phelan

eRA COMMONS USER NAME (credential, e.g., agency login): PHELANJ

POSITION TITLE: Staff Scientist

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
The Ohio State University, Columbus, OH	B.S.	06/2004	Biological Sciences
University of Cincinnati, Cincinnati, OH	Ph.D.	04/2012	Immunology
National Cancer Institute, NIH, Bethesda, MD	Post-doc	06/2020	Lymphoma Biology

A. Personal Statement

The goal of my research is to elucidate the molecular pathogenesis of lymphoid malignancies in order to better diagnose and treat these aggressive forms of cancer. To do so, I leverage functional genomic screening technologies to identify novel biomarkers, find new drug targets, decipher mechanisms of disease pathogenesis, and elucidate pathways critical for drug resistance. Pairing genome wide CRISPR screens with proteomic profiling techniques, I discovered a novel mode of oncogenic signaling present in diffuse large B cell lymphoma (DLBCL) that is exceptionally sensitive to the targeted BTK kinase inhibitor, ibrutinib. Moreover, in collaboration with our intramural CCR colleagues, we developed a novel application of a protein proximity assay to detect this mode of oncogenic signaling in ibrutinib-responsive DLBCL patient samples. We are currently optimizing these assays and pairing them with comprehensive multiplatform next generation sequencing approaches to identify molecular distinct forms of lymphoma, reveal unique therapeutic targets, and test novel combinations of therapies in genetically homogeneous disease subsets.

I am currently supported by the intramural NIH funding of Drs. Louis M. Staudt & Mark Roschewski

B. Positions, Scientific Appointments, and Honors

Positions

2020-Present	Staff Scientist, Lymphoid Malignancies Branch, National Cancer Institute, Bethesda, MD
2018– 2020	Research Fellow, Lymphoid Malignancies Branch, National Cancer Institute, Bethesda, MD
2013– 2018	Postdoctoral Fellow, Lymphoid Malignancies Branch, National Cancer Institute, Bethesda, MD
2006– 2012	Graduate Student, Division of Immunobiology, Cincinnati Children's Research Foundation, Cincinnati, OH

Honors

2019	Center for Cancer Research, National Cancer Institute, Outstanding Postdoctoral Fellow Finalist
2016	Host for laboratory visit by Governor Larry Hogan, NIH
2011	The Ohio State's Comprehensive Cancer Center, Pelotonia Graduate Fellowship

C. Contributions to Science

1. **Elucidating the Function of Non-Oncogenes in Normal and Malignant Hematopoiesis.** My dissertation focused on the role of transcription factors in normal blood cell development and malignant transformation. Using transgenic mouse models, I identified novel requirements for Gfi1 in early murine hematopoietic progenitors and in human T cell acute lymphoblastic leukemia (T-ALL). My work helped to establish the precedent that transcription factors could have separable programs at similar stages of cellular differentiation. We demonstrated this by deleting Gfi1 at different stages of T cell development and in T cell leukemias using various promoter specific Cre recombinase mouse strains. We found that in early hematopoietic progenitors, Gfi1 opposed HoxA9 in myeloid progenitors, whereas it was required to integrate Notch signaling in lymphoid progenitors. However, at later stages of development, and in T-ALL, Gfi1 opposed p53 function and thus protected T cells from DNA damage and apoptosis. Notably, these functions could be targeted with novel antisense oligonucleotide therapies and loss of GFI1 synergized with DNA damaging agents.
   - **a)** **Phelan JD,** Saba I, Zeng H, Kosan C, Messer MS, Olsson HA Fraszczak J, Hildeman DA, Aronow BJ, Möröy T, Grimes HL. Growth factor independent-1 maintains Notch1-dependent transcriptional programming of lymphoid precursors. PLoS Genet 2013; 9: e1003713. PMC3772063
   - **b)** Khandanpour C*, **Phelan JD***, Vassen L, Schutte J, Chen R, Horman SR Gaudreau MC, Krongold J, Zhu J, Paul WE, Dührsen U, Göttgens B, Grimes HL, Möröy T. Growth factor independence 1antagonizes a p53-induced DNA damage response pathway in lymphoblastic leukemia. Cancer Cell 2013; 23: 200-214. PMC3597385
     * These authors contributed equally
   - **c**) Velu CS, Chaubey A, **Phelan JD**, Horman SR, Wunderlich M, Guzman ML Jegga AG, Zeleznik-Le NJ, Chen J, Mulloy JC, Cancelas JA, Jordan CT, Aronow BJ, Marcucci G, Bhat B, Gebelein B, Grimes HL. Therapeutic antagonists of microRNAs deplete leukemia-initiating cell activity. J Clin Invest 2014; 124: 222-236. PMC3871218
   - **d)** **Phelan JD**, Shroyer NF, Cook T, Gebelein B, Grimes HL. Gfi1-cells and circuits: unraveling transcriptional networks of development and disease. Curr Opin Hematol 2010; 17: 300-307.PMC2910316

2. **Defining the Genetic Causes of Lymphoma.** In my postdoctoral studies, I wanted to improve my understanding of lymphoid malignancies, and joined the laboratory of Louis Staudt who was testing targeted precision medicine agents in lymphoma. Aggressive lymphomas are diagnosed by shared histological features but display extreme heterogeneity in response to therapy. Efforts to molecularly subtype diffuse large b cell lymphoma (DLBCL) had identified unique transcriptional signatures that predict response to standard immuno-chemotherapy and yielded three major subtypes of DLBCL known as activated B-cell like (ABC), germinal center like (GCB) and unclassified DLBCL. Yet, varying response rates to targeted inhibitors suggested further diversity of biological mechanisms existed within gene expression subtypes. To capture the genetic landscape of DLBCL tumors, we performed an integrative structural genomic study combining exome-seq, transcriptome analysis, and DNA copy number analysis with nearly 600 patient samples. To identify functional variants in this dataset, I performed both gain-of-function open reading frame (ORF) screens and loss-of-function CRISPR screens, each in combination with targeted inhibitors of various survival pathways in DLBCL cell lines. By pairing these functional screening data with the genomic datasets, we created a genetic classifier algorithm which identified new subclasses of DLBCL.
   - **a)** Schmitz R*, Wright GW*, Huang DW*, Johnson CA*, **Phelan JD**, Wang JQ, Roulland S, Kasbekar M, Young RM, Shaffer AL, Hodson DJ, Xiao W, Yu X, Yang Y, Zhao H, Xu W, Liu X, Zhou B, Du W,Chan WC, Jaffe ES, Gascoyne RD, Connors JM, Campo E, Lopez-Guillermo A, Rosenwald A, Ott G, Delabie J, Rimsza LM, Tay Kuang Wei K, Zelenetz AD, Leonard JP, Bartlett NL, Tran B, Shetty J,Zhao Y, Soppet DR, Pittaluga S, Wilson WH, Staudt LM. Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma. N Engl J Med 2018; 378: 1396-1407. PMC6010183
     * These authors contributed equally
   - **b)** Wright GW, Huang DW, **Phelan JD**, Coulibaly ZA, Roulland S, Young RM, Wang JQ, Schmitz R, Morin RD, Tang J, Jiang A, Bagaev A, Plotnikova O, Kotlov N, Johnson CA, Wilson WH, Scott DW, and Staudt LM. A Probabilistic Classification Tool for Genetic Subtypes of Diffuse Large B Cell Lymphoma with Therapeutic Implications. Cancer Cell 2020; 37: 1-18. PMC *in progress*

c) Young RM, **Phelan JD**, Shaffer AL 3rd, Wright GW, Huang GW, Schmitz R, Johnson C, Oellerich T, Wilson WH and Staudt LM. Taming the Heterogeneity of Aggressive Lymphomas for Precision Therapy. Annual Review of Cancer Biology 2019; 3: 429-455. PMC *in progress*

3. **Discovery of Oncogenic Mechanisms of Aggressive Lymphomas.** Discovering disease relevant mutations is one hurdle to improving treatment methods for aggressive lymphomas. However, understanding how those mutations influence complex signaling and transcriptional networks and which mutations respond to a given therapy is a much larger hurdle. In the publications below, I employed functional proteogenomic discovery pipelines to dissect the oncogenic signaling modules in DLBCL. By integrating both genome-wide CRISPR Cas9 screens with novel proteomic proximity profiling methods, I discovered divergent survival signaling downstream of the B cell receptor (BCR) in DLBCL. In GCBs and Burkitt lymphomas, I found a form of oncogenic signaling that we termed "toncogenic" for its similarity to normal germinal center B cells in activating PI3K and mTOR. In ABCs, I discovered a multiprotein complex consisting of the MyD88, TLR9 and the BCR (My-T-BCR) that controls oncogenic NF-kB signaling. The My-T-BCR is exquisitely sensitive to inhibition of BTK and its presence in DLBCL patient samples correlates with clinical response to the BTK inhibitor, ibrutinib. These studies provide a roadmap for the rational development and implementation of targeted inhibitors of the BCR in future lymphoma clinical trials.
   a) **Phelan JD***, Young RM*, Webster DE, Roulland S, Wright GW, Kasbekar M, Shaffer AL 3rd, Ceribelli M, Wang JQ, Schmitz R, Nakagawa M, Bachy E, Huang DW, Ji Y, Chen L, Yang Y, Zhao H, Yu X, Xu W, Palisoc MM, Valadez RR, Davies-Hill T, Wilson WH, Chan WC, Jaffe ES, GascoyneRD, Campo E, Rosenwald A, Ott G, Delabie J, Rimsza LM, Rodriguez FJ, Estephan F, Holdhoff M,Kruhlak MJ, Hewitt SM, Thomas CJ, Pittaluga S, Oellerich T, Staudt LM. A multiprotein supercomplex controlling oncogenic signalling in lymphoma. Nature 2018; 560: 387-391. PMC6201842
   * These authors contributed equally
   b) Shaffer AL, **Phelan JD**, Wang JQ, Huang DW, Wright GW, Kasbekar M, Choi J, Young RM, Webster DE, Yang Y, Zhao H, Yu X, Xu W, Roulland S, Ceribelli M, Zhang X, Wilson KM, Chen L, McKnight C, Klumpp-Thomas C, Thomas CJ, Haupl B, Oellerich T, Rae Z, Kelly MC, Ahn IE, Sun C, Gaglione EM, Wilson WH, Wiestner A, and Staudt LM. Overcoming Acquired Epigenetic Resistance to BTK Inhibitors. Blood Cancer Discov. 2021. doi: 10.1158/2643-3230.BCD-21-0063
   c) Dersh D, **Phelan JD**, Gumina ME, Wang B, Arbuckle JH, Holly J, Kishton RJ, Markowitz TE, Seedhom MO, Fridlyand N, Wright GW, Huang DW, Ceribelli M, Thomas CJ, Lack JB, Restifo NP, Kristie TM, Staudt LM, Yewdell JW. Genome-wide Screens Identify Lineage- and Tumor-Specific Genes Modulating MHC-I- and MHC-II-Restricted Immunosurveillance of Human Lymphomas. Immunity 2021. Jan 12;54(1):116-131. PMC7874576
   d) Choi J, **Phelan JD**, Wright GW, Häupl B, Huang DW, Shaffer AL 3rd, Young RM, Wang Z, Zhao H, Yu X, Oellerich T, Staudt LM. Regulation of B-cell receptor-dependent NF-κB signaling by the tumor suppressor KLHL14. Proc Natl Acad Sci 2020. Mar 17;117(11):6092-6102. PMC7084139

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1Zgwfh6On2D5K/bibliography/public/

Invited Talks

Seminars

National Center for Advancing Translational Sciences, Division of Pre-Clinical Innovation. Rockville, MD. "Improving Precision Medicine through Functional Proteogenomic Screens", September 2019

British Columbia Cancer Agency, BCCA Research Seminar Series. Vancouver, Canada. "Functional Proteogenomic Screens Reveal Mechanisms of Oncogenic Signaling in Lymphoma", February 2019

Children's National Research Foundation, Center for Cancer and Immunology Research. Washington D.C. "Functional Proteogenomic Screens Reveal Mechanisms of Oncogenic Signaling in Lymphoma", October 2018

Cancer & Blood Disease Institute, Cincinnati Children's Hospital. Cincinnati, OH. "Predicting Response to Lymphoma Therapies through Functional & Structural Genomics", June 2017

Food and Drug Administration, Center for Drug Evaluation and Research, Office of Biotechnology Products Seminar Series. Silver Spring, MD. "Genomic-scale CRISPR screen identifies essential mechanisms of survival and drug resistance in diffuse large B cell lymphoma", November 2015.

Meeting Speaker

European School of Haematology, Annual International Conference on New Concepts in Lymphoid Malignancies: Focus on Aggressive Lymphomas. Dublin, Ireland. "Functional Proteogenomic Screens Reveal Mechanisms of Oncogenic Signaling in Lymphoma", September 2018

Cambridge Lymphoma Biology International Symposium. St. John's College, Cambridge, U.K.
Keynote: "Therapy of Lymphoma Inspired by Functional and Structural Genomics", July 2018

NIH Immunology Interest Group Training Workshop. Leesburg, VA. "Mechanism of Response to BTK-targeted Therapy of Aggressive Lymphomas Revealed by CRISPR Screens", September 2017

NIH Immunology Interest Group Training Workshop. Potomac, MD. "A synthetic lethal genomic-scale CRISPR screen in diffuse large B cell lymphoma", September 2015.